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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: :
Muriel SERRADEIL ALBALAT, et al. Docket No.: 2002FR302
Serial No.: to be Assigned :
Filed: January 28, 2005 :
For: Process For The Preparation Of Primary Amines

Transmittal Letter
Notification of Amendments Under PCT Article 34


Mail Stop:
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Preliminary to the examination of the above-identified application, an Amendment was filed under Article 34 of the Patent Cooperation Treaty prior to the International Preliminary Examination. Please note that the attached pages 46-55 for claims 1- 16 were filed with the European Patent Office. We enclose an English translation of the claims for your convenience.

Applicant respectfully requests submission of these pages before examination of the application and before entry of the Preliminary Amendment.

Respectfully submitted,


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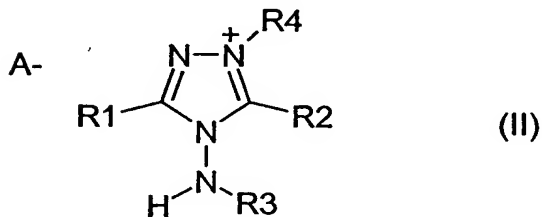
1. Process for the preparation of primary amines of formula (I):

(1)

R3 represents

- a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by one or more hydroxyl groups, amino groups, alkoxy groups including from 1 to 6 carbon atoms or aryl groups including from 6 to 10 carbon atoms, the aryl groups optionally being substituted by one or more linear or branched alkyl groups including from 1 to 6 carbon atoms or by one or more alkoxy groups including from 1 to 6 carbon atoms or by one or more phenyl groups,
- a cycloalkyl group including from 5 to 7 carbon atoms which is optionally substituted by one or more linear or branched alkyl groups including from 1 to 6 carbon atoms by or one or more alkoxy groups including from 1 to 6 carbon atoms,
- an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more linear or branched alkyl groups including from 1 to 6 carbon atoms, by one or more alkoxy groups including from 1 to 6 carbon atoms or by one or more phenyl groups,

by reaction of a triazolium salt of formula (II):



in which

R1 and R2, which are identical or different, represent

- hydrogen,
- a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, $-(OCH_2CH_2O)_nR'''$ groups in which n represents an integer ranging from 1 to 4 and R''' is a linear or branched alkyl group including from 1 to 4 carbon atoms, -O-aryl groups including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups, or -O-aralkyl groups including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups;
- an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups;
- an aryl group including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,

R3 has the meaning already indicated,

R4 represents

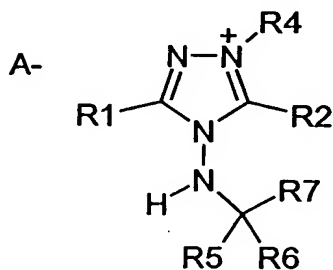
- a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by a -COOH radical or a -COOR''' group in which R''' represents a linear or branched alkyl radical including from 1 to 4 carbon atoms,
- an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or a -COOH radical or a -COOR''' group in which R''' represents a linear or branched alkyl radical including from 1 to 4 carbon atoms,
- a residue of an organic polymer functionalized by an alkylating group,

A represents

- a halogen,
- an alkylsulphonate group including from 1 to 6 carbon atoms which is optionally substituted by one or more halogen groups,
- an arylsulphonate group including from 6 to 10 carbon atoms which is optionally substituted by one or more halogen groups or linear or branched alkyl groups including from 1 to 4 carbon atoms,
- an alkyl sulphate group including from 1 to 6 carbon atoms,
- a hydrogen sulphate group,
- a hemisulphate group,
- a perchlorate group, or
- a hydroxide group,

with a hydride, to obtain the amine of formula (I), which is isolated, if desired.

2. Process according to Claim 1, characterized in that the R3 group comprises an asymmetric carbon α to the nitrogen.
3. Process according to Claim 1 or 2, characterized in that the triazolium salt of formula (II) corresponds to the formula (IIa):



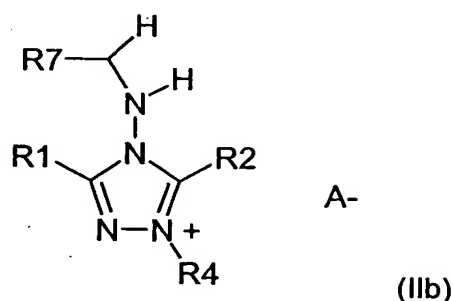
(IIa)

in which

- R1, R2, R4 and A have the meaning already indicated and R5 represents

- a hydrogen,
- a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, hydroxyl groups or amino groups,

- a cycloalkyl group including from 3 to 7 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms,
- 5 - an aryl group including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- 10 - an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- R6 represents
- 15 - a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, hydroxyl groups or amino groups,
- 20 - a cycloalkyl group including from 3 to 7 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms,
- 25 - an aryl group including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- 30 - an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- 30 - an aminotriazolium group of formula



in which R1, R2, R4 and A have the meaning already indicated,

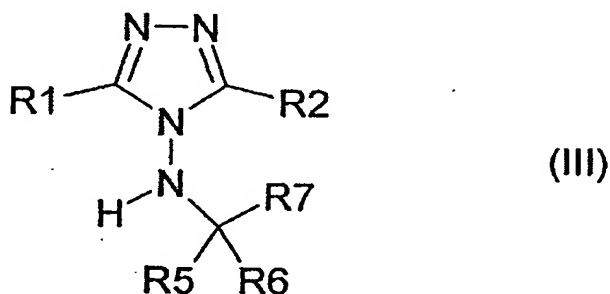
5 R7 represents

- a hydrogen,
- a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms, hydroxyl groups or amino groups,
- 10 - a cycloalkyl group including from 3 to 7 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms,
- an aryl group including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- 15 - an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups, or
- 20

25 R5 and R6 can form, together with the carbon atom to which they are bonded, a ring comprising 5 to 7 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms,

it being understood that the carbon carrying the R5, R6 and R7 radicals must be asymmetric.

4. Process according to one of Claims 1 to 3, characterized in that the compound of formula (II) corresponds to the formula (IIa) defined above in Claim 3 and, in addition, the said compound of formula (IIa) is prepared by reaction of a compound of formula (III):

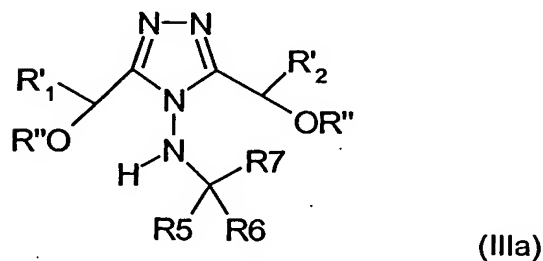


in which

R1, R2, R5, R6 and R7 have the meaning already indicated in Claim 3,

with an agent for the quaternization of a nitrogen, to produce the compound of formula (IIa), which is isolated, if desired, or which is employed directly in the following stage.

5. Process according to one of Claims 1 to 4, characterized in that the compound of formula (II) corresponds to the formula (IIa) defined above in Claim 3 and, in addition, the said compound of formula (IIa) is prepared by reaction of a compound of formula (IIIa):



in which

R5, R6 and R7 have the meaning already indicated in Claim 3,

R'1 and R'2 represent

- a linear or branched alkyl group including from 1 to 6 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms,
- 5 - an aryl group including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups, or
- 10 - an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups, and

R'' represents

- hydrogen,
- 15 - a linear or branched alkyl group including from 1 to 6 carbon atoms,
- an aryl group including from 6 to 10 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- 20 - an aralkyl group including from 7 to 16 carbon atoms which is optionally substituted by one or more alkoxy groups including from 1 to 6 carbon atoms or linear or branched alkyl groups including from 1 to 6 carbon atoms or phenyl groups,
- 25 - a $-(\text{CH}_2\text{CH}_2\text{O})_n\text{R}'''$ group in which n represents an integer ranging from 1 to 4 and R''' is a linear or branched alkyl group including from 1 to 4 carbon atoms,

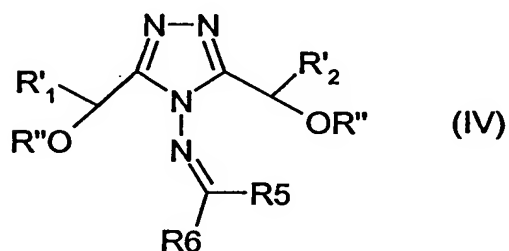
30 with an agent for the quaternization of a nitrogen, to produce the compound of formula (IIa), which is isolated, if desired, or which is employed directly in the following stage.

- 35 6. Process according to Claim 5, characterized in that the compound of formula (IIIa) is additionally prepared by reaction of an organometallic compound of formula

R7-M

in which R7 has the meaning already indicated in Claim 3 and M represents an
MgX or CeX₂ group in which X represents a halogen atom and M represents a
5 metal, such as Li, Cu or (1/2) Zn,

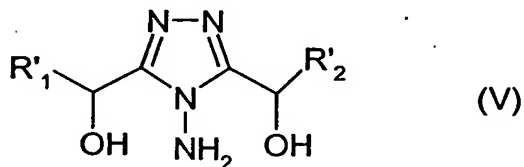
with a compound of formula (IV)



10 in which R'1, R'2 and R'' have the meaning already indicated in Claim 4 and R5
and R6 have the meaning already indicated in Claim 3, it being understood that,
when R'' is a hydrogen, at least one of R5 and R6 is an optionally substituted aryl
group,

15 to produce the compound of formula (IIIa), which is isolated, if desired, or which
is employed directly in the following stage.

- 20 7. Process according to Claim 6, characterized in that the compound of formula (IV)
is prepared by etherification and reaction of a compound of formula (V):



25 in which R'1 and R'2 have the meaning already indicated in Claim 4, with a
compound of formula



in which R5 and R6 have the meaning already indicated in Claim 3,

to produce the compound of formula (IV), which is isolated, if desired, or which is employed directly in the following stage.

- 5
8. Process according to Claim 7, characterized in that the etherification takes place before the reaction of the compound of formula (V) with the compound of formula $O=CR_5R_6$.
- 10
9. Process according to Claim 7, characterized in that the etherification takes place after the reaction of the compound of formula (V) with the compound of formula $O=CR_5R_6$, it being understood that at least one of R5 and R6 represents an optionally substituted aryl group.
- 15
10. Process according to Claim 5, characterized in that the compound of formula (IIa) is additionally prepared by reduction by the action of a metal hydride on a compound of formula (IV) defined above in Claim 6 or by hydrogenation of the said compound of formula (IV), it being understood that R5 cannot, in this case, represent hydrogen.
- 20
11. As novel intermediates for preparing an amine of formula $H_2N-CHR_6R_7$, the following compounds:
- 25
- 4-[(R)-1-Ethyl-2,2-dimethoxyethylamino]-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole
 - 4-[(S)-1-Ethyl-2,2-dimethoxyethylamino]-(S,S)-3,5-bis(1-ethoxyethyl)-1,2,4-triazole
 - 30 - 4-[(R)-1-Ethyl-2,2-dimethoxyethylamino]-(S,S)-3,5-bis(1-ethoxyethyl)-1,2,4-triazole
 - 4-(1-Phenyl-2,2-dimethoxyethylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole
 - 4-(1-Ethyl-2,2-dimethoxyethylamino)-(S,S)-3,5-bis(1-(2-methoxyethyl)ethyl)-1,2,4-triazole
 - 35 - 4-(1-Ethylbutylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole

- 4-(1-Ethylisobutylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole
- 4-(1-Phenylpropylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole
- 4-(1-Phenylethylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole
- (Hexyl-3,4-diamino)-4,4'-bis[(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole].

5

12. As novel intermediates for preparing an amine of formula $H_2N-CR_5R_6R_7$, the following compounds:

- N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-2,2-dimethoxyethylimine
- 10 - N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]butylimine
- N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]isobutylimine
- N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-1-(ethoxycarbonyl)methylimine
- N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-1-phenylethylimine
- 15 - N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-1-methyl-2,2-dimethoxyethylimine
- Bis[N-[(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazol-4-yl]methylimine]
- N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-2,2-dimethoxyethylimine
- N-[(S,S)-3,5-Bis(1-(2-methoxyethoxy)ethyl)-1,2,4-triazol-4-yl]-2,2-dimethoxyethylimine.
- 20

13. Process according to one of Claims 4 to 6, characterized in that, in addition, the stereoisomers of formula (III) or (IIIa) are separated by, optionally chiral, high performance liquid chromatography.

25

14. Process according to either of Claims 3 and 5, characterized in that, in addition, the diastereoisomers of formula (IIa) are separated by crystallization.

30

15. An enantiomerically pure diastereoisomer of a compound of formula (IIa) obtained according to the process of Claim 14.

35 16. Enantiomerically pure 1-benzyl-4-[(R)-1-phenyl-2,2-dimethoxyethylamino]-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazolium bromide according to claim 15.